Effect of eplerenone in patients with heart failure and reduced ejection fraction: Potential effect modification by abdominal obesity

Insight from EMPHASIS-HF trial

Arnaud Olivier[1,2,3], Bertram Pitt[4], Nicolas Girerd[1,3,5,6], Zohra Lamiral[1,3], Jean-Loup Machu[1, 3], John J. V. McMurray[7], Karl Swedberg[8], Dirk J. van Veldhuisen[9], Timothy J. Collier[10], Stuart J. Pocock[10], Patrick Rossignol[1,3,5,6], Faiez Zannad[1,2,3,5,6] and Anne Pizard*[1,3,5,6]

[1] Inserm CIC Plurithématique 1433, UMRS 1116 Inserm, CHRU Nancy, Vandoeuvre-lès-Nancy, France.

[2] cardiovascular departments, CHRU Nancy, Vandoeuvre-lès-Nancy, France.

[3] F-CRIN INI-CRCT, France

[4] University of Michigan, School of Medicine, Ann Arbor, USA.

[5] Université de Lorraine, Nancy, France.

[6] Fédération de Recherche 3209, Vandoeuvre-lès-Nancy, France.

[7] University of Glasgow, Glasgow, United Kingdom.

[8] University of Gothenburg, Gothenburg, Sweden.

[9] University Medical Centres, Groningen, the Netherlands.

[10] London School of Hygiene and Tropical Medicine, London, United Kingdom.

Short title: Abdominal adiposity as biomarker for MRA efficacy

*** Corresponding author:**

Anne Pizard, PhD, CR1 Inserm

Inserm UMR-S1116, CIC-Plurithématique 1433, CHRU-Nancy

4 rue du Morvan, 54500 Vandoeuvre-lès-Nancy, France

Tel: + 33 (0)3 83 15 52 97

anne.pizard@inserm.fr

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ejhf.792

Abstract

Aims An excessive production of aldosterone influences outcome in patients with heart failure (HF) and in obese patients. Findings from laboratory studies suggest that chronic aldosterone blockade maybe more beneficial in abdominally obese HF prone rats. In the current study, we investigated if the clinical response to a mineralocorticoid receptor antagonist in mildly symptomatic HF patients varied by abdominal obesity.

Methods and Results 2587 NYHA class II, low ejection fraction HF patients enrolled in the EMPHASIS-HF trial were randomly assigned to eplerenone and placebo. In this post-hoc analysis, patients were categorized according to waist circumference (normal if WC < 102 cm in men and < 88 cm women; abdominal obesity if NWCe 102cm in men and e88cm women). The potential statistical interaction between the treatment and WC was assessed on the primary endpoint of death from cardiovascular causes or hospitalization for HF and other secondary endpoints. Over a median follow-up of 21 months, a significant benefit of eplerenone for the primary outcome was noted in both normal (HR 0.77, CI95% 0.61-0.98, p=0.03) and increased (HR 0.48, CI95% 0.37-0.63, p<0.0001) WC subgroups but the latter patients appeared to receive greater benefit than patients with normal WC (p for interaction 0.01). This suggests a significant quantitative (treatment effect varies in magnitude by subgroup, but is always in same direction) rather than a qualitative interaction (direction of the treatment effect varies by subgroup) between eplerenone and WC in the adjusted analysis. Mean doses of eplerenone, blood pressure and serum potassium changes and adverse events were similar between WC subgroups.

Conclusion In EMPHASIS-HF, eplerenone improved outcomes in HFrEF patients with and without abdominal obesity, although the benefit appeared to be more pronounced among those with abdominal obesity. The findings are potentially hypothesis generating and needs to be replicated in other HFrEF populations.

Keywords Abdominal obesity; Heart failure with reduced ejection fraction; Eplerenone

Introduction

Obesity is recognized as a cardiovascular risk factor and the worldwide epidemics of obesity parallels the one observed for HF.[1-3] It is associated with increased risk of cardio renal disease, including hypertension, coronary artery disease and adverse cardiac remodelling (left ventricular hypertrophy and dilation), and progression towards HF.[4] On another hand obese subjects have higher aldosterone levels, which may result in mineralocorticoid receptor (MR) over activation. Reciprocally, higher aldosterone levels have been implicated in the development and maintenance of obesity.[5-7]

Mineralocorticoid receptor antagonist (MRA) therapy improves outcomes in patients with chronic systolic HF with mild symptoms (EMPHASIS-HF trial), acute symptomatic systolic HF in post myocardial infarction (EPHESUS trial) and in severe NYHA stage III-IV systolic HF (RALES trial).[8-10] However, to the best of our knowledge the influence of established overweight or obesity on the response to MRAs is unknown. Studies in obese non-HF patients with or without associated metabolic disorder[11] suggested that MRA therapy improved left ventricular function and myocardial abnormalities with concurrent decreases of circulating fibrotic markers. Knowing that visceral fat is a source of serum aldosterone and that several experimental studies[7, 12-14] have implicated aldosterone as an important mediator of obesity-related cardiovascular risk, we have recently published the first experimental data suggesting that as compared to leaner counterparts, viscerally-obese heart failure prone rats may further benefit from chronic MRA treatment [15]. Yet no study has specifically evaluated whether clinical response to a MRA over a long follow-up period might be better in HF patients with *vs.* without abdominal obesity.

In this context, we sought for the first time to evaluate the interaction between increased adiposity estimated by the waist circumference (WC) and body mass index (BMI, as reference obesity measurement parameter) and the clinical benefit from the MR antagonist eplerenone in patients with congestive HF receiving recommended therapy for systolic HF (ejection fraction below 35%) and enrolled in the EMPHASIS-HF trial.[10]

Methods

The design, patient eligibility criteria, study procedure and main results of the EMPHASIS-HF study have been previously reported.[10] In brief, in this randomized double-blind trial,

patients with New York Heart Association class II heart failure and an ejection fraction of no more than 35% (HFrEF) were randomly assigned to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy.

Study outcomes

The same primary and secondary outcomes were used in the current analysis as in the main study.[10] Briefly, the primary outcome was the composite of death from cardiovascular causes or first hospitalization for HF. The pre-specified adjudicated secondary outcomes were respectively all cause death, cardiovascular death and hospitalization for HF. For continuous variables, the baseline value was defined according to the EMPHASIS-HF statistical analysis plan as the measurement that was made on the closest date prior to the study medication starting date. If there were more than one measurement made on the same date, the average value of these data was calculated and used as the baseline measurement.

Because the following variables did not fulfil the assumption of log-linearity, WC and BMI were not analysed as continuous variables but as categorical variables.

Waist circumference

Baseline measurement of WC was performed by a tape measure placed around subject's bare abdomen just above subject's hipbone, at the level of the subject's navel, when the relaxed subject exhaled. The tape measure was positioned parallel to the floor without compressing the subject's skin. Values were considered aberrant and were excluded from the data analysis when WC < 60 cm.

Subjects were divided into two WC groups according to the American Heart Association (AHA) defined cutoffs.[16] Men and women with WC values <102 and <88 cm, respectively, were considered to have a normal WC (NWC group), whereas those with WC values e102 and e88 cm respectively were considered to have high WC (HWC group) and harbour an abdominal obesity. Subjects were further categorized according to WC quintiles taking into account sex differences.

Body mass index

Body mass index is defined as the weight in kilograms divided by the square of the height in meters (kg/m^2). BMI values were considered missing when height or weight measures were not reported. Obesity was defined according to the WHO BMI classification (http://apps.who.int/bmi/index.jsp?introPage=intro_3.html): BMIe30 kg/m^2 were classified was obese

patients while BMI values <30 kg/m^2 characterized normal weighted and overweight patients.

Statistical analysis

Waist circumference and BMI were the key explanatory variables. Continuous variables are expressed as mean ± standard deviation (m±SD), categorical variables as frequencies (percentage). Comparisons of baseline characteristics between WC or BMI groups were performed using Student t-test or Mann-Whitney or chi-Square test as required. Risk probabilities were calculated using the Kaplan-Meier method and plotted as survival curves.

Hazard ratios and respective 95% confidence intervals were estimated using univariable and multivariable Cox proportional hazard regression models. Assumptions of log-linearity, absence of multi-colinearity and hazards proportionality were thoroughly verified.

Interactions between BMI or WC and eplerenone effect on outcomes were assessed by introducing an interaction term (BMI or WC variable*eplerenone) in crude (i.e. BMI or WC, eplerenone, BMI or WC*eplerenone) and adjusted models. The following candidate covariates were considered for adjustment: age, gender, heart rate, systolic blood pressure, left ventricular ejection fraction, QRS duration, medical history (hospitalization for HF, hypertension, angina pectoris, myocardial infarction, coronary artery angioplasty, coronary artery bypass surgery, atrial fibrillation or flutter, diabetes mellitus, stroke), device therapy (implantable cardioverter-defibrillator, cardiac-resynchronization therapy, implantable cardioverter-defibrillator with cardiac resynchronization), blood sodium, blood potassium, estimated glomerular filtration rate and use of diuretics, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), beta-blockers, and lipid-lowering agents. Among these candidate covariates, variables significantly associated with the outcome of interest with a p-value < 0.15 on univariable cox regression [17] were further selected using an interactive backward selection process. Only the covariates associated with the outcome of interest with a p-value < 0.05 were retained in multivariable models.

In addition, we evaluated the functional form of the interaction between treatment and WC/BMI with regards to the risk of outcomes using WC/BMI as a non-linear continuous variable. To do so, we used restricted cubic splines and plotted the hazard ratios of treatment effect according to WC/BMI calculated from the Cox model.

Adverse events and those leading to permanent study drug withdrawal were presented according to WC or BMI category groups.

Statistical interaction has come into increasing use in trial analysis. Given the low power of interaction tests, selected a priori a 0.10 cut-off threshold for the interaction p value has been used. As a consequence, a p-value of <0.05 was considered statistically significant for the main effects and <0.10 for the interaction terms.

All analyses were performed using software SAS version 9.4 (SAS Institute Inc., Cary, N.C., USA).

Results

Clinical characteristics

Of the 2737 patients randomized in EMPHASIS-HF, 2579 were included in the WC analysis (158 patients had a missing or implausible WC value). Median WCs were 100 cm (IQR92-108) and 94 cm (IQR85-104) in men and women respectively and 1295 patients (50.2%) had a HWC (abdominal obesity if WC e102 cm for men and e88 cm for women). The remaining 1284 individuals had a NWC (if WC <102 cm for men and <88 cm for women) *(Table1, TableS1)*. Patients with a HWC had more obesity-related disorders such as hypertension, atrial fibrillation and diabetes mellitus, as compared to patients with a NWC (*Table1)*. However, there were no clinically significant differences between patients allocated to eplerenone or placebo within the two WC subgroups *(Table S1)*.

Of the 2737 patients randomized in EMPHASIS-HF, 2722 were included in the BMI analysis (15 patients had a missing or implausible BMI value). The median BMI was 27 kg/m^2 (IQR24-30) and 739 patients (27.1%) had a global obesity with BMIe30 kg/m^2 and 1983 (72.9%) a BMI<30 kg/m^2. Like patients with a HWC, those with a high BMI had more obesity-related disorders, as compared to patients with a BMI<30 kg/m^2 *(Table1)*.

The median follow-up duration among all patients was 21 months (IQR: 10 to 33 months).

Eplerenone safety profile across subgroups

Adverse events leading to eplerenone withdrawal occurred in 101(15.7%) NWC patients as compared to 74 (11.5%) HWC patients (p=0.034) leading to a p of interaction value of 0.01 (*TableS2*). Hyperkalaemia adverse events and hyperkalaemia leading to study drug discontinuation occurred equally in WC and BMI eplerenone subgroups respectively (*TableS2*).

Mean doses achieved across subgroups

The mean dose of eplerenone did not different between WC subgroups (p=0.67). Among patients assigned to eplerenone, 61.4 % and 62.3% of the HWC and NWC groups, respectively, received the highest daily dose (50 mg daily, p=0.81). Likewise, the mean dose of eplerenone did not differ between BMI subgroups (p=0.79) and 60.8% of the BMIe30kg/m^2 patients against 61.6% of the BMI<30kg/m^2 groups received the highest daily dose eplerenone (50 mg daily, p=0.96).

Effect of eplerenone on clinical outcomes

Overall, there were fewer primary endpoints in the eplerenone group in EMPHASIS-HF (HR 0.63, 95% CI 0.52-0.75). This was also the case for other outcomes, including all-cause mortality (HR 0.76, 95% CI 0.61-0.94) cardiovascular mortality (HR 0.73, 95% CI 0.58-0.93) and hospitalization for heart failure (HR 0.59, 95% CI 0.48-0.73) (*Figures 1 and 2*).

When analysing according to WC and BMI anthropomorphic subgroups, no differential effect of the treatment was observed on blood pressure, heart rate, body weight and serum potassium levels, expressed as changes from baseline to month 1 and month 5-post randomisation (data not shown).

Interaction between abdominal obesity and the effects of eplerenone

The modifying effect of abdominal obesity on the impact of eplerenone for each outcome is shown in figures 1 and 2. The effect of eplerenone on the primary outcome was significant in both patients with HWC (multivariable HR 0.48, 95% CI 0.37-0.63) and in patients with a NWC (multivariable HR 0.77, 95% CI 0.61-0.98), but significantly stronger in the HWC group as demonstrated by a p value for the interaction of 0.01 *(Figure 1A, Figure 2A*).

Importantly, abdominal obesity i.e. HWC was not associated with the primary outcome in the placebo group (multivariable HR 0.96, 95% CI 0.76-1.20) whereas it was associated with lower rates for the primary events in the eplerenone group (multivariable HR 0.60, 95% CI 0.45-0.80), resulting in a significant interaction between eplerenone and HWC in the adjusted analysis (p=0.01).

Overall, similar patterns were observed for the secondary outcomes but the interaction between eplerenone and HWC reached statistical significance only for "Death from cardiovascular causes" and "Hospitalization for HF" secondary outcomes (p for interaction

0.09 and 0.07 respectively) (*Figure2*). In addition, we identified a significant interaction in men between treatment and WC within the model using restricted cubic splines (Figure3) (p value for the interaction p=0.025 in the adjusted model, Figure3A). The shape of the association is difficult to assess in women given the wide confidence intervals resulting from the small number of patients within the subset of female patients. In this subset, the interaction did not reach statistical significance (p=0.30 in the adjusted model, Figure3B). Likewise the interaction between treatment and BMI for both genders using restricted cubic splines did not reached significance (p=0.15 in the adjusted model, Figure3C).

Overall both WC groups derived significant benefit from eplerenone for the primary outcome and hospitalization for heart failure with quantitatively greater benefits derived from the treatment in patients with abdominal obesity from the HWC subgroup. A lower dropout rate was observed in patients randomized to eplerenone when they had HWC, which could contribute to the higher treatment effect observed in this subgroup and further suggests a net higher benefit to risk ratio in the HWC group. A sensitivity analysis censoring the follow-up up to the time of permanent drug discontinuation yielded interaction still suggesting a higher benefit to risk ratio in the HWC group.

While analysing the EMPHASIS-HF population using WC quintiles, we observed lower HR for the primary outcome in patients within the 3rd to 5th quintile (i.e. e97cm in men and e90cm in women) than in patients within the first two quintiles (*TableS3*) with a significant p value for interaction between eplerenone and WC of p=0.09. Interestingly, multivariable HR in the 3rd to 5th quintile ranged from 0.47 (95% CI 0.32-0.71) to 0.53 (95% CI 0.34-0.82) whereas the HRs of the first two quintiles were 0.70 (95% CI 0.49-1.00) and 0.94 (95% CI 0.64-1.37). Of note, these cut-offs (i.e. e97 cm in men and e90 cm in women) within the EMPHASIS-HF population were below and above the cut-offs defining abdominal obesity in men and women respectively.

Interaction between of BMI and the effects of eplerenone

The benefit of eplerenone on the rate of the primary outcome seemed to be greater in obese (BMIe30kg/m^2) patients (multivariable HR 0.49, 95% CI 0.35-0.71) than in patients with a BMI<30kg/m^2 (multivariable HR 0.69, 95% CI 0.57-0.83) but the difference is not as marked as for WC and the p-value of interaction between BMI and eplerenone was greater than 0.10 (p=0.11, *Figure 2, Table2)*. Similar observations were done for secondary outcomes, with no

significant interaction in the adjusted analyses between BMI and the effect of eplerenone (*Table2*). When analysed according to the median BMI value of 27kg/m^2, the benefit of eplerenone on the rate of the primary outcome was greater in patients with BMIe27kg/m^2 (multivariable HR 0.50, 95% CI 0.38-0.65) than in patients with BMI<27kg/m^2 (multivariable HR 0.76, 95% CI 0.61-0.94; p for interaction P=0.018) (*Table S4*). These results of BMI analyses with a cut-off defined at 27 kg/m² and 30 kg/m² (Tables S4 and 2 respectively) are confirmed by the shape of the association in adjusted model between Eplerenone and the primary outcome according to the value of BMI when used as continuous variable (Figure 3C). Risk of CVD or HHF is higher for values around 25 kg/m², while it decreases until a value of 30 kg/m², and then remains steady (Figure 3C). Likewise, the benefit of eplerenone on the rates of hospitalization for HF was greater in patients with a BMIe27kg/m^2 (multivariable HR 0.44, 95% CI 0.33-0.62) than in patients with a BMI<27kg/m^2 (multivariable HR 0.68, 95% CI 0.52-0.88; p for interaction =0.051) (*Table S4*).

Discussion

The main finding of our *post hoc* analysis of the EMPHASIS-HF data suggest that patients with HF and reduced ejection fraction and mild symptoms who have abdominal obesity, derive greater benefit from eplerenone than those who are not obese or overweight. All HFrEF patients derived benefits from eplerenone in the EMPHASIS-HF trial, but the greater benefits afforded by eplerenone in HWC patients substantiated by the significant interaction between WC and eplerenone for three out of the four studied outcomes. This characterized for the first time a quantitative rather than a qualitative interaction between adiposity and the response to MRA therapy. Importantly, this greater benefit occurred with the use of similar doses of eplerenone and overall the benefit/risk ratio was more favourable since the rate of adverse events was not different among WC subgroups. Altogether this *post hoc* analysis of EMPHASIS-HF suggests that abdominal obesity estimated by waist circumference measurement could be a simple and straightforward classifier identifying a subset of patients with HF and reduced ejection fraction that might derive greater benefit from MRA therapy. Despite the known adverse impact of obesity on most of the HF risk factors, our results suggest that a better prognosis of patients with abdominal obesity i.e. obesity paradox. Thus our results suggest for the first time that part of the known obesity paradox observed in HF trial might be explained by the greater benefits derived by obese patients from their HF MRA treatment.

The deleterious impact of excessive aldosterone/MR activation in the heart has been extensively documented this past decade. Both cortisol and aldosterone adversely affect the cardiovascular events *via* the activation of the mineralocorticoid receptors in the heart, blood vessels, kidney and other sites.[18] Notably, high levels of aldosterone promote the development of interstitial cardiac fibrosis, promote platelet aggregation and contribute to endothelial dysfunction in part by reducing nitric-oxide bioavailability and favour hypertension, chronic kidney disease as well as concentric left ventricular hypertrophy in the general community.[19] Furthermore MR activation in macrophages has been demonstrated to promote coronary and systemic inflammation particularly in the initial response to reperfusion injury after ischemic injury. [20, 21] Collectively those studies have justified the targeting of MR as new approach for the treatment of heart failure patients. [8, 10, 22] The mechanism of action of MRAs in HF is multiple including anti-inflammatory, anti-fibrotic and anti-remodelling properties and decrease in sympathetic drive and improves heart-rate variability. [23,24, 25] It could be in part attributed to the increased MR activation and more pronounced production of its ligands in the failing human heart. [4, 26, 27]

Experimental and clinical studies suggest that MR over activation in hyperphagic conditions [28] and high fat diet induced obesity may precipitate cardiac remodelling and HF development. [13, 29, 30] In fact, all components of the renin-angiotensin aldosterone system are expressed in adipose tissue and their gene expression has been found increased in adipose tissues of both obese animal models and obese humans. [7, 31, 32] The increments in body weight and overall obesity are known to result from chronic positive energy balance, a condition which is known to increase the MR expression and further favour the development of adipose tissue inflammation and fibrosis. [29] We recently demonstrated that chronic eplerenone treatment delayed the cardiac remodelling and HF onset in both lean and obese spontaneously hypertensive heart failure rats but that obese rats presenting a higher aldosterone level further benefited from MRA treatment through improvement of their obesity, dyslipidaemia and myocardial fibrosis. [15] Further experimental studies have demonstrated that the benefits of MR blockade included reduced obesity-related cardiac fibrosis, coronary micro vascular disorders, and cardiac oxidative stress and systemic inflammation. [13, 30] Small exploratory clinical studies further suggested beneficial effects of spironolactone on left ventricular dysfunction in obese individuals without other comorbidities and in patients with metabolic syndrome, support our observation of a more pronounced clinical benefit of MRA therapy in overweight to obese

individuals. [11, 23] It also suggests that overweight to obese HF patients may derive great benefit from MRA at least in part because of their high inflammatory and fibrotic clinical status. [33-35]

This is of strong interest when considering that in the USA approximately ½ to 2/3 of the HF patients are overweight or obese.[36] Interestingly aldosterone was proposed to promote adipogenesis by inducing peroxisome proliferator activated receptor γ expression, while increased adiposity is known to have adverse effects on LV structure and function, and other risk factors of HF including hypertension and coronary artery diseases.[13, 37] Thus, although speculative in clinic but based on strong experimental evidence, one tentative explanation of the better response to eplerenone of HF patients with abdominal obesity might be that these patients have higher aldosterone levels associated with hyper-secretion of trophic factors from the visceral adipose tissue.[5, 38] The observed better discriminative power of the WC parameters in defining the best responder group of HFrEF to eplerenone as compared to BMI, might be explained in part by the fact that the RAAS has been described to have variable activity depending on the adipose tissue location. A high RAAS activity has been reported in abdominal adipocytes, which are more closely associated with the aldosterone biosynthesis and where angiotensinogen and angiotensin II receptor gene expression levels are high. A lower RAAS activity was reported in gluteofemoral adipose tissue, which may explain why the fat from this latter location is less metabolically active.[39]

Adipose tissue is considered as an endocrine organ influencing the maintenance of the body metabolic and inflammatory homeostasis especially when located in close vicinity with the heart, kidney, liver and the skeletal muscle. The development of visceral fat tissue results in crucial endocrine interactions with those vital organs that may lead to their structural and functional alterations.[40,41]

While largely used to classify obesity, a clear limitation of BMI is that it is unable to distinguish between increased body fat content and increased lean body mass (breakdown of body composition) and cannot indicate where the adiposity preferentially develops as it is accountable for the characterization of a global obesity. Our results highlight the different relevance of those two anthropometric parameters, and confirm that BMI and WC are not characterizing the same type of adiposity. Altogether a total of 668 EMPHASIS patients were "misclassified" when using BMI: 626 of them were non-obese (BMI<30kg/m^2) but harboured an abdominal obesity (HWC) and 42 of them were classified obese (BMIe 30kg/m^2) but had NWC. Those patients are the one discriminating the results between BMI and WC parameters

and leading to the statistically significant results for the interaction in WC but not in BMI subgroups. All types of adipose fat depot are not alike and can differ by their location (gynoid, android, visceral, subcutaneous, overall) and degrees (from overweight up to morbid obesity). Numerous imaging tools, such as dual-energy X-ray absorptiometry, bioelectrical impedance analysis and magnetic resonance imaging and anthropometric measure like BMI and WC can discriminately evaluate them. Whether imaging data would better define the fat deposition thus better refine the subsequent risk is beyond the scope of our study, but WC is such an easy cost-less biomarker to access that its use in general clinic should be warranted.
Moreover weight variation in HF patients is very much dependant on fluid retention, and the resulting congestion may mostly impact BMI and in a lesser extend WC. This suggests that the latter parameter might be more reliable in the context of HF. Our results suggest for the first time that the specific location of the excess of adiposity represents an important matter when treating HF patients.

While still requiring replication, the differential findings reported for WC and BMI with regards to the patient response to eplerenone, is consistent with the large body of literature suggesting that depending on their location, adipose tissue deposits present distinct metabolic and inflammatory properties. While both subcutaneous and visceral adipose tissues are considered as endocrine organs, visceral adipose tissue has especially been shown to secrete adipocytokines and other vasoactive substances including aldosterone [24, 25] and has been associated with higher mortality than overall obesity defined by BMI. [42, 43] The increase in either or both types of fat deposit (subcutaneous and visceral) participates in the development of an abdominal obesity, which is readily and easily measurable with WC.

Interestingly, our data show no differential effect of the treatment on blood pressure, heart rate, body weight and serum potassium levels, according to WC anthropomorphic subgroups, an hyperkalaemia adverse events including those leading to study drug discontinuation occurred equally in WC eplerenone subgroups. In addition, hypotension, adverse events leading to eplerenone withdrawal occurred significantly less frequently in patients with increased abdominal adiposity. Taken together, our results suggest that the benefit/risk ratio of eplerenone therapy is higher in patients with abdominal obesity.
Even though not verify here (the absence of available bio samples precluded us to reconcile the levels of MR ligands and the degree of abdominal adiposity in the EMPHASIS-HF

patients), in clinic plasma aldosterone concentration correlated with increased adiposity measured by BMI and is associated with the development of metabolic syndrome with increased WC in the Framingham population and in African-American population. [26,27] It was thus expected that EMPHASIS obese patients presented worse clinical characteristics as compared to their lean counterparts. While overweight and obesity are demonstrated pejoratively impacting the risk of cardiovascular diseases in the general population, a reduced mortality in HF population with higher BMI values has been demonstrated and referred as obesity paradox. [44, 45] Clark et al demonstrated such paradox in advanced HF cohort (LVEF <25%) and increased WC was mostly associated with improved outcomes in advanced HF. [36, 42]

Although our results suggest an improved response to MRA treatment of EMPHASIS HF patients as one out of many other possible contributors to the obesity paradox. Indeed, such paradox, also described in other pathophysiologic conditions, varies according to i) the aetiology of the wide range of clinical phenotypes observed in different HF cohorts restricting the protective effect of obesity to patients with non ischemic HF; ii) the patient gender; iii) the patient age; iv) the LVEF; v) the cumulative exposure to excess adiposity and resulting metabolic reserve; vi) the presence of diabetes. [35,37, 45-49]

One could extrapolate that what is called the HF obesity paradox [37, 42, 44, 46-48] described in other HF trials might also be a consequence of HF therapy being more effective in obese patients. This is at least suggested by the results of our study where abdominally obese patients are better responders to mineralocorticoid receptor antagonism then leaner participants. Interestingly, this potential better response to RAAS inhibitors based therapy is also suggested in the placebo group where more than 90% of the enrolled patients are already treated with ACE inhibitor or ARB and where those with increased adiposity did not demonstrated significant association with worsen outcomes. In other reports mentioning this HF obesity paradox phenomenon the association of BMI with outcomes was studied while adjusting for the background medical therapy, but the interaction of BMI with therapy are yet to be reported. Thus in-depth evaluation of the proposed paradoxical effect of obesity in HF patients as compared to the general population taking into account exposure to therapy is now required to validate our hypothesis. Future studies should explore the potential relationship between RAAS inhibition and the obesity paradox taken into account that our study was based on the cut-offs for WC and BMI that have been defined for their predictive value of health risks only but not for their capacity to predict the response to a given drug. Further analysis in larger population should be considered to challenge and potentially redefine those

cut-offs in order to use WC and BMI as stratifying biomarkers when prescribing MRA therapy.

Our findings should be regarded as hypothesis generating for future studies that should be designed to confirm whether HF patients with increased adiposity i.e. patients characterized by elevated MR ligand secretion, are potentially the best responders to MRA therapy. Because EMPHASIS-HF patients presenting an abdominal obesity derive greater benefit from eplerenone, future investigation should evaluate how the greater response to MRA therapy could contribute to and partly explain the so-called "obesity paradox" observed in HF populations. [50,37, 41] Our results call upon further investigations of obesity-associated measurements as potential straightforward classifiers predicting the therapeutic response to MRAs in HF patients and in other CV diseases and their respective risk factors for which MR activation has been implicated. More specifically, it is tempting to explore whether increased adiposity may also help identify responders to MRA therapy among HF patients with preserved ejection fraction, an important category of HF patients in much need for novel effective therapies. Indeed recently reported neutral results on clinical trials using MRA on HF patients with preserved ejection fraction have been yet explained by international geographic variation.[51] In regard of our results, the event rates should be analysed according to difference in anthropomorphic parameters of the enrolled patients in Russia and Georgia and in American patients in the TOPCAT trial.[22]

Acknowledgement: The authors wish to thank Kevin Duarte for his collaborative input and Dr Hervé Kempf for the in-depth and critical reading of the manuscript.

Funding: This work was supported by Inserm and the European program HOMAGE (#305507) The clinical trial sponsor was not involved in the analysis, interpretation of data, writing of the report or the decision to publish.

Conflict of interest Statement: no conflict of interest to be declared

References

1. De Pergola G, Nardecchia A, Giagulli VA, Triggiani V, Guastamacchia E, Minischetti MC, Silvestris F. Obesity and heart failure. Endocr Metab Immune Disord Drug Targets 2013;**13**(1):51-7.
2. Kenchaiah S, Pocock SJ, Wang D, Finn PV, Zornoff LA, Skali H, Pfeffer MA, Yusuf S, Swedberg K, Michelson EL, Granger CB, McMurray JJ, Solomon SD, Investigators C. Body mass index and prognosis in

patients with chronic heart failure: insights from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Circulation 2007;**116**(6):627-36.
3. Schocken DD, Benjamin EJ, Fonarow GC, Krumholz HM, Levy D, Mensah GA, Narula J, Shor ES, Young JB, Hong Y, American Heart Association Council on E, Prevention, American Heart Association Council on Clinical C, American Heart Association Council on Cardiovascular N, American Heart Association Council on High Blood Pressure R, Quality of C, Outcomes Research Interdisciplinary Working G, Functional G, Translational Biology Interdisciplinary Working G. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. Circulation 2008;**117**(19):2544-65.
4. Mizuno Y, Yoshimura M, Yasue H, Sakamoto T, Ogawa H, Kugiyama K, Harada E, Nakayama M, Nakamura S, Ito T, Shimasaki Y, Saito Y, Nakao K. Aldosterone production is activated in failing ventricle in humans. Circulation 2001;**103**(1):72-7.
5. Caprio M, Feve B, Claes A, Viengchareun S, Lombes M, Zennaro MC. Pivotal role of the mineralocorticoid receptor in corticosteroid-induced adipogenesis. FASEB J 2007;**21**(9):2185-94.
6. Funder JW, Reincke M. Aldosterone: a cardiovascular risk factor? Biochim Biophys Acta 2010;**1802**(12):1188-92.
7. Lastra G, Sowers JR. Obesity and cardiovascular disease: role of adipose tissue, inflammation, and the renin-angiotensin-aldosterone system. Horm Mol Biol Clin Investig 2013;**15**(2):49-57.
8. Pitt B, Williams G, Remme W, Martinez F, Lopez-Sendon J, Zannad F, Neaton J, Roniker B, Hurley S, Burns D, Bittman R, Kleiman J. The EPHESUS trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. Eplerenone Post-AMI Heart Failure Efficacy and Survival Study. Cardiovasc Drugs Ther 2001;**15**(1):79-87.
9. Pitt D. ACE inhibitor co-therapy in patients with heart failure: rationale for the Randomized Aldactone Evaluation Study (RALES). Eur Heart J 1995;**16 Suppl N**:107-10.
10. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B, Group E-HS. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;**364**(1):11-21.
11. Kosmala W, Przewlocka-Kosmala M, Szczepanik-Osadnik H, Mysiak A, Marwick TH. Fibrosis and cardiac function in obesity: a randomised controlled trial of aldosterone blockade. Heart 2013;**99**(5):320-6.
12. Caprio M, Antelmi A, Chetrite G, Muscat A, Mammi C, Marzolla V, Fabbri A, Zennaro MC, Feve B. Antiadipogenic effects of the mineralocorticoid receptor antagonist drospirenone: potential implications for the treatment of metabolic syndrome. Endocrinology 2011;**152**(1):113-25.
13. Guo C, Ricchiuti V, Lian BQ, Yao TM, Coutinho P, Romero JR, Li J, Williams GH, Adler GK. Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. Circulation 2008;**117**(17):2253-61.
14. Hirata A, Maeda N, Hiuge A, Hibuse T, Fujita K, Okada T, Kihara S, Funahashi T, Shimomura I. Blockade of mineralocorticoid receptor reverses adipocyte dysfunction and insulin resistance in obese mice. Cardiovasc Res 2009;**84**(1):164-72.
15. Youcef G, Olivier A, Nicot N, Muller A, Deng C, Labat C, Fay R, Rodriguez-Guéant R-M, Leroy C, Jaisser F, Zannad F, Lacolley P, Vallar L, Pizard A. A preventive and chronic mineralocorticoid recptor antagonism preferentially benefited to obses SHHF rats. British Journal of Pharmacology 2016;**173**(11):1805-1819.
16. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ, American College of Cardiology/American Heart Association Task Force on Practice G, Obesity S. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol 2014;**63**(25 Pt B):2985-3023.
17. Derksen S, Keselman HJ. Backward, forward and stepwise automated subset selection algorithms : Frequency of obtaining authentic and noise variables. British Journal of Mathematical and Statistical Psychology 1992;**45**:265-282.
18. Weber KT. Aldosterone in congestive heart failure. N Engl J Med 2001;**345**(23):1689-97.
19. Buglioni A, Cannone V, Cataliotti A, Sangaralingham SJ, Heublein DM, Scott CG, Bailey KR, Rodeheffer RJ, Dessi-Fulgheri P, Sarzani R, Burnett JC, Jr. Circulating aldosterone and natriuretic peptides in the general community: relationship to cardiorenal and metabolic disease. Hypertension 2015;**65**(1):45-53.
20. Young MJ, Rickard AJ. Mineralocorticoid receptors in the heart: lessons from cell-selective transgenic animals. J Endocrinol 2015;**224**(1):R1-13.

21. Gilbert KC, Brown NJ. Aldosterone and inflammation. Curr Opin Endocrinol Diabetes Obes 2010;**17**(3):199-204.
22. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau JL, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM, Pitt B. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation 2015;**131**(1):34-42.
23. Kosmala W, Jedrzejuk D, Derzhko R, Przewlocka-Kosmala M, Mysiak A, Bednarek-Tupikowska G. Left ventricular function impairment in patients with normal-weight obesity: contribution of abdominal fat deposition, profibrotic state, reduced insulin sensitivity, and proinflammatory activation. Circ Cardiovasc Imaging 2012;**5**(3):349-56.
24. Marzolla V, Armani A, Zennaro MC, Cinti F, Mammi C, Fabbri A, Rosano GM, Caprio M. The role of the mineralocorticoid receptor in adipocyte biology and fat metabolism. Mol Cell Endocrinol 2012;**350**(2):281-8.
25. Whaley-Connell A, Sowers JR. Oxidative stress in the cardiorenal metabolic syndrome. Curr Hypertens Rep 2012;**14**(4):360-5.
26. Ingelsson E, Pencina MJ, Tofler GH, Benjamin EJ, Lanier KJ, Jacques PF, Fox CS, Meigs JB, Levy D, Larson MG, Selhub J, D'Agostino RB, Sr., Wang TJ, Vasan RS. Multimarker approach to evaluate the incidence of the metabolic syndrome and longitudinal changes in metabolic risk factors: the Framingham Offspring Study. Circulation 2007;**116**(9):984-92.
27. Rossi GP, Belfiore A, Bernini G, Fabris B, Caridi G, Ferri C, Giacchetti G, Letizia C, Maccario M, Mannelli M, Palumbo G, Patalano A, Rizzoni D, Rossi E, Pessina AC, Mantero F, Primary Aldosteronism Prevalence in hYpertension Study I. Body mass index predicts plasma aldosterone concentrations in overweight-obese primary hypertensive patients. J Clin Endocrinol Metab 2008;**93**(7):2566-71.
28. Youcef G, Olivier A, L'Huillier CP, Labat C, Fay R, Tabcheh L, Toupance S, Rodriguez-Gueant RM, Bergerot D, Jaisser F, Lacolley P, Zannad F, Laurent V, Pizard A. Simultaneous characterization of metabolic, cardiac, vascular and renal phenotypes of lean and obese SHHF rats. PLoS One 2014;**9**(5):e96452.
29. Armani A, Cinti F, Marzolla V, Morgan J, Cranston GA, Antelmi A, Carpinelli G, Canese R, Pagotto U, Quarta C, Malorni W, Matarrese P, Marconi M, Fabbri A, Rosano G, Cinti S, Young MJ, Caprio M. Mineralocorticoid receptor antagonism induces browning of white adipose tissue through impairment of autophagy and prevents adipocyte dysfunction in high-fat-diet-fed mice. FASEB J 2014;**28**(8):3745-57.
30. Bender SB, DeMarco VG, Padilla J, Jenkins NT, Habibi J, Garro M, Pulakat L, Aroor AR, Jaffe IZ, Sowers JR. Mineralocorticoid receptor antagonism treats obesity-associated cardiac diastolic dysfunction. Hypertension 2015;**65**(5):1082-8.
31. Massiera F, Bloch-Faure M, Ceiler D, Murakami K, Fukamizu A, Gasc JM, Quignard-Boulange A, Negrel R, Ailhaud G, Seydoux J, Meneton P, Teboul M. Adipose angiotensinogen is involved in adipose tissue growth and blood pressure regulation. FASEB J 2001;**15**(14):2727-9.
32. Whaley-Connell A, Johnson MS, Sowers JR. Aldosterone: role in the cardiometabolic syndrome and resistant hypertension. Prog Cardiovasc Dis 2010;**52**(5):401-9.
33. Hu G, Jousilahti P, Antikainen R, Katzmarzyk PT, Tuomilehto J. Joint effects of physical activity, body mass index, waist circumference, and waist-to-hip ratio on the risk of heart failure. Circulation 2010;**121**(2):237-44.
34. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. N Engl J Med 2002;**347**(5):305-13.
35. Levitan EB, Yang AZ, Wolk A, Mittleman MA. Adiposity and incidence of heart failure hospitalization and mortality: a population-based prospective study. Circ Heart Fail 2009;**2**(3):202-8.
36. Clark AL, Fonarow GC, Horwich TB. Waist circumference, body mass index, and survival in systolic heart failure: the obesity paradox revisited. J Card Fail 2011;**17**(5):374-80.
37. Lavie CJ, McAuley PA, Church TS, Milani RV, Blair SN. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. J Am Coll Cardiol 2014;**63**(14):1345-54.
38. Mathieu P, Boulanger MC, Despres JP. Ectopic visceral fat: a clinical and molecular perspective on the cardiometabolic risk. Rev Endocr Metab Disord 2014;**15**(4):289-98.
39. Feliciano Pereira P, Eloiza Priore S, Bressan J. Aldosterone: a cardiometabolic risk hormone? Nutr Hosp 2014;**30**(6):1191-202.
40. Bastien M, Poirier P, Lemieux I, Despres JP. Overview of epidemiology and contribution of obesity to cardiovascular disease. Prog Cardiovasc Dis 2014;**56**(4):369-81.
41. Lavie CJ, Sharma A, Alpert MA, De Schutter A, Lopez-Jimenez F, Milani RV, Ventura HO. Update on Obesity and Obesity Paradox in Heart Failure. Prog Cardiovasc Dis 2015.
42. Gupta PP, Fonarow GC, Horwich TB. Obesity and the obesity paradox in heart failure. Can J Cardiol 2015;**31**(2):195-202.

574 43. Sahakyan KR, Somers VK, Rodriguez-Escudero JP, Hodge DO, Carter RE, Sochor O, Coutinho T,
575 Jensen MD, Roger VL, Singh P, Lopez-Jimenez F. Normal-Weight Central Obesity: Implications for Total and
576 Cardiovascular Mortality. Ann Intern Med 2015.
577 44. Lavie CJ, Milani RV, Artham SM, Patel DA, Ventura HO. The obesity paradox, weight loss, and
578 coronary disease. Am J Med 2009;**122**(12):1106-14.
579 45. Zamora E, Lupon J, Enjuanes C, Pascual-Figal D, de Antonio M, Domingo M, Comin-Colet J, Vila J,
580 Penafiel J, Farre N, Alonso N, Santesmases J, Troya M, Bayes-Genis A. No benefit from the obesity paradox for
581 diabetic patients with heart failure. Eur J Heart Fail 2016.
582 46. Nasir K, Campbell CY, Santos RD, Roguin A, Braunstein JB, Carvalho JA, Blumenthal RS. The
583 association of subclinical coronary atherosclerosis with abdominal and total obesity in asymptomatic men. Prev
584 Cardiol 2005;**8**(3):143-8.
585 47. Reis JP, Allen N, Gunderson EP, Lee JM, Lewis CE, Loria CM, Powell-Wiley TM, Rana JS, Sidney S,
586 Wei G, Yano Y, Liu K. Excess body mass index- and waist circumference-years and incident cardiovascular
587 disease: the CARDIA study. Obesity (Silver Spring) 2015;**23**(4):879-85.
588 48. Shah R, Gayat E, Januzzi JL, Jr., Sato N, Cohen-Solal A, diSomma S, Fairman E, Harjola VP, Ishihara
589 S, Lassus J, Maggioni A, Metra M, Mueller C, Mueller T, Parenica J, Pascual-Figal D, Peacock WF, Spinar J,
590 van Kimmenade R, Mebazaa A, Network G. Body mass index and mortality in acutely decompensated heart
591 failure across the world: a global obesity paradox. J Am Coll Cardiol 2014;**63**(8):778-85.
592 49. Zamora E, Lupon J, de Antonio M, Urrutia A, Coll R, Diez C, Altimir S, Bayes-Genis A. The obesity
593 paradox in heart failure: is etiology a key factor? Int J Cardiol 2013;**166**(3):601-5.
594 50. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity
595 paradox on prevalence and prognosis in heart failure. JACC Heart Fail 2013;**1**(2):93-102.
596 51. Kristensen SL, Kober L, Jhund PS, Solomon SD, Kjekshus J, McKelvie RS, Zile MR, Granger CB,
597 Wikstrand J, Komajda M, Carson PE, Pfeffer MA, Swedberg K, Wedel H, Yusuf S, McMurray JJ. International
598 geographic variation in event rates in trials of heart failure with preserved and reduced ejection fraction.
599 Circulation 2015;**131**(1):43-53.
600
601
602
603

Figure legends

Figure 1 Cumulative Kaplan-Meier estimates of rates of the primary and secondary outcomes according to the four studied groups PLA, Placebo; EPL, Eplerenone; WC, waist circumference with NWC for normal WC group (WC < 102 cm for men and <88 cm for women) and HWC for high WC group characterized by the presence of an abdominal obesity (WCe 102 cm for men and e88 cm for women).

Figure 2 Hazard ratios for studied outcomes with eplerenone versus placebo in overall population and according to specified subgroups of WC and BMI.

The subgroups are based on baseline demographic and clinical characteristics. Values within the entire population are presented in gray. Values within the normal ranges of waist circumference (NWC i.e. WC<102/88 cm for men and women respectively) and body mass index (BMI<30 kg/m^2) are presented in black and increased values in white (HWC i.e. WC e102/88 cm for men and women respectively and BMIe30kg/m^2). Presented data are the results of multivariable model analysis adjusted for statistically significant covariates among those listed and tested in the statistical analysis section. Thus the total number of patients (2340) is inferior in this figure to the number of 2579 in Table 2 as the result of missing value in some patients.

Figure 3: Eplerenone treatment effect according to morphometric parameters using restricted cubic spline

Restricted cubic splines were drawn for the composite primary outcome to model the interaction between treatment and WC (A-B) or BMI (C) when both morphometric parameters were used as a continuous variable. Interactions are presented for male (A), women (B) and for both genders (C) in adjusted models. The continuous lines represent the hazard ratio and the dotted lines represent the confidence limits for the considered HR.